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A Guide to Screening for Autoimmune Diseases in Patients With Vulvar Lichen Sclerosus

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ABSTRACT

Background: The aetiology of vulvar lichen sclerosus (VLS) remains unknown. However, there is evidence that in addition to a genetic predisposition, autoimmunity contributes to the pathogenesis.

Objectives: The objective of this study was to determine the prevalence of autoimmune disease and positive autoantibody serology in patients with VLS.

Methods: A VLS database in Sydney, Australia, was retrospectively reviewed. A diagnosis of VLS was required for inclusion in the study. Data collected included demographics, comorbidities including any personal history of autoimmune disease, family history of autoimmune disease, and the results from autoantibody testing. A total of 2243 females with VLS were included in this study.

Results: Autoimmune disease was found in 24.5% and 34.6% of children and adults with VLS, respectively. The most prevalent autoimmune conditions were psoriasis, Hashimoto's thyroiditis, lichen planus, and vitiligo. Antinuclear antibodies were common and found in 31.0% of patients. Thyroid peroxidase and thyroglobulin antibodies were present in 16.1% and 18.9% of cases, respectively. Thyroid function, determined by thyroid stimulating hormone, was abnormal in 8.2% of patients. 5.3% of patients had positive parietal cell antibodies, and 5.9% had low vitamin B12 levels.

Conclusions: This work provides support that VLS is of an autoimmune aetiology, and that there is an association between VLS and autoimmune diseases. The high proportion of patients with an abnormal thyroid test, positive thyroid antibodies, and intrinsic factor and gastric parietal cell antibodies with low vitamin B12 levels, warrants screening for thyroid disease and pernicious anaemia in patients with VLS. Initial autoimmune screening in VLS can be rationalised to TSH, vitamin B12 levels, intrinsic factor and parietal cell antibodies. Thyroid antibodiy testing shouls be performed in hypothyroid patients.

1 | Introduction

Lichen sclerosus is a chronic inflammatory skin condition that preferentially affects anogenital skin. Lichen sclerosus occurs across all ages and genders, including prepubescent children. Vulvar lichen sclerosus (VLS) causes characteristic porcelain-white plaques that can be associated with atrophy, erosion, purpura and fissuring of the vulva and perianal skin. VLS is a rare

condition [1, 2], although recent studies have described a rising incidence [3, 4]. Severe, intractable pruritus is the most common symptom [5–8].

The pathogenesis of VLS is currently unknown but is likely multifactorial [9, 10]. The most compelling current perspective is that VLS is an autoimmune condition with a genetic predisposition [11]. Case–control studies have shown a significantly higher prevalence of autoimmune disease in VLS patients [12–15]. Two recent studies, representing the largest studies to date, have shown a high prevalence of autoimmune thyroid disease compared to controls [12, 15]. Other autoimmune conditions more prevalent in VLS include pernicious anaemia [13, 14], alopecia areata [14], psoriasis [12], and vitiligo [12, 14]. The general population prevalence of penicious anaemia is around 0.1%, although it is more common in older people [16]. In Australia, coeliac disease has a prevalence of approximately 1% in the community [17].

Studies in 1974 and 1981 found that VLS patients have significantly higher levels of gastric parietal cell, intrinsic factor, and thyroid antibodies compared to controls [13, 18]. Thyroid autoantibodies are the most common serology found in VLS patients [8, 19–22], but this has not been consistently reported [14]. Unfortunately, all studies evaluating the prevalence of autoantibodies to date have been small (< 400 patients) and the results variable [2, 8, 13, 14, 18–23].

Current clinical guidelines advocate testing for autoimmune disease only if symptoms are present [24, 25]. Whilst it is generally recommended that thyroid function testing, and thyroid autoantibody screens be undertaken [25], it is unclear if screening for other autoantibodies should be undertaken. To address this current gap in knowledge, we conducted a retrospective study evaluating the prevalence of autoimmune conditions and serology in a large cohort of patients with VLS. Within this paper, the term “female” is used to refer to biological sex. Our aim was to determine the prevalence of positive autoantibody serology in VLS to inform future clinical guidelines for screening of asymptomatic disease.

2 | Materials and Methods

A database from a single institution in Australia was reviewed retrospectively. Online records from 2008 to 2023 were analysed. Female patients with either a biopsy-proven or a clinical diagnosis of VLS were included in this study. Patients were excluded from the analysis if they only had extragenital disease, or if they had not provided consent. In addition to baseline demographics, data collected included a personal history of autoimmune disease, a family history of autoimmune disease, the autoantibody screens conducted, and the results of serological tests. Children were defined as less than or equal to 12 years of age and the adult group included all ages greater than 12 years. Data were collected and stored using the Research Electronic Data Capture (REDCap) software. Local ethics approval was obtained (2023/ETH00719).

Descriptive results were given as numbers and percentages. Data were analysed using SPSS Statistics for windows, version 29 (SPSS Inc., Chicago, Ill., USA).

3 | Results

A total of 2359 VLS patient records were included in this study out of 2672 files (88.3%). VLS was biopsy confirmed in 66.4% of patients. Biopsies were rarely conducted in children. The median duration of follow-up was 3 years, with a minimum of 0 years and a maximum of 33 years. Two hundred and nine patients were lost to follow-up or received further care elsewhere. The median age at symptom onset was 52 years old, with a range from 5 months to 91 years ($n = 1443$). The median age at diagnosis was 55 years old, with a minimum and maximum age of 1 and 92 years, respectively ($n = 2243$). A total of 116 out of 2359 patients had no date of diagnosis recorded and therefore they were excluded from further analysis that was divided into paediatric and adult cohorts. In this study, there were 159 children and 2084 adults.

3.1 | Autoimmune Disease

A history of autoimmune disease was present in 24.5% of patients diagnosed as children and 34.6% of patients diagnosed with VLS as adults. In patients diagnosed as children, two patients had two autoimmune conditions, and one patient had three. The most common autoimmune conditions were psoriasis, vitiligo and Hashimoto's thyroiditis (Table 1). In adults with an autoimmune disease, 17.8% had two, 5.8% had three and 1.5% had four or more autoimmune conditions. In adult patients, the most common autoimmune conditions were psoriasis, Hashimoto's thyroiditis, lichen planus, vitiligo and Graves' disease (Table 2).

3.2 | Family History of Autoimmunity

A family history of autoimmune disease was reported in 22.6% of children and 8.5% of adults. Autoimmune conditions that were seen in the relatives of paediatric patients were psoriasis, autoimmune thyroid disease (not specified further), and Hashimoto's thyroiditis (Table 3). Psoriasis and autoimmune thyroid disease were the most prevalent familial autoimmune diseases in adult patients (Table 4). In one paediatric case and 11 adult patients, an autoimmune family history was noted, but

TABLE 1 | The prevalence of autoimmune diseases in patients diagnosed with vulvar lichen sclerosus as children ($n = 159$). Children were defined as ≤ 12 years.

Autoimmune disease	Number (%)
Psoriasis	28 (17.6)
Vitiligo	5 (3.1)
Hashimoto's thyroiditis	3 (1.9)
Coeliac disease	2 (1.3)
Scleroderma	2 (1.3)
Alopecia areata	1 (0.7)
Lichen planus	1 (0.7)
Rheumatoid arthritis	1 (0.7)

TABLE 2 | The prevalence of autoimmune diseases in patients diagnosed with vulvar lichen sclerosus as adults ($n = 2084$). Adults were defined as > 12 years.

Autoimmune disease[a]	Number (%)
Psoriasis	336 (16.1)
Hashimoto's thyroiditis	117 (5.5)
Lichen planus	99 (4.8)
Vitiligo	44 (2.1)
Graves' disease	38 (1.8)
Coeliac disease	33 (1.6)
Sjogren's syndrome	31 (1.5)
Rheumatoid arthritis	27 (1.3)
Inflammatory arthritis[b]	24 (1.2)
Pernicious anaemia/autoimmune gastritis	21 (1.0)
Polymyalgia rheumatica	19 (0.9)
Scleroderma/morphea	19 (0.9)
Inflammatory bowel disease[c]	16 (0.8)
Crohn's disease	15 (0.7)
Alopecia areata	14 (0.7)
Autoimmune thyroid disease (not specified)	11 (0.5)
Systemic lupus erythematous (SLE)	11 (0.5)
Type 1 diabetes mellitus	9 (0.4)
Ulcerative colitis	8 (0.4)
Frontal fibrosing alopecia	8 (0.4)
Autoimmune hepatitis/autoimmune cholangitis[d]	7 (0.3)
Sarcoidosis	6 (0.3)
Cutaneous/discoid lupus	5 (0.2)
Eosinophilic oesophagitis	5 (0.2)
Immune thrombocytopenic purpura	5 (0.2)
Multiple sclerosus	5 (0.2)

[a]Rare autoimmune conditions (≤ 3 patients) are not shown in this table. Rare autoimmune diseases observed in this cohort included: Addison's disease, antiphospholipid syndrome, mucous pemphigoid, ankylosing spondylitis, autoimmune renal tubular acidosis, dermatomyositis, inclusion body myositis, necrotising autoimmune myositis, giant cell arteritis, Henloch-Schönlein purpura, IgA nephropathy, autoimmune autonomic ganglionopathy, autoimmune iritis, autoimmune pancreatitis, autoimmune tendonitis, chronic autoimmune pericarditis, chronic inflammatory demyelinating polyradiculopathy, Churg-Strauss syndrome, Goodpasture syndrome, incomplete Behcet's syndrome, myasthenia gravis, obstetric lupus, and subcorneal pustular dermatosis.
[b]Inflammatory arthritis included seronegative arthritis, undifferentiated connective tissue disease, and palindromic rheumatism.
[c]Inflammatory bowel disease included collagenous colitis, lymphocytic colitis, and microscopic colitis.
[d]This group included autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, and primary biliary cholangitis.

no specific conditions were described. A family history of lichen sclerosus occurred in 13.8% of paediatric patients and 4.8% of adult patients.

TABLE 3 | The prevalence of autoimmune diseases in relatives of patients diagnosed with vulvar lichen sclerosus as children, defined as ≤ 12 years ($n = 159$).

Autoimmune disease	Number (%)
Psoriasis	19 (11.9)
Autoimmune thyroid disease (not specified)	8 (5.0)
Hashimoto's thyroiditis	6 (3.8)
Coeliac disease	3 (1.9)
Graves' disease	3 (1.9)
Systemic lupus erythematous (SLE)	3 (1.9)
Lichen planus	2 (1.3)
Vitiligo	2 (1.3)
Alopecia areata	1 (0.6)
Autoimmune iritis	1 (0.6)
Dermatomyositis	1 (0.6)
Inflammatory bowel disease	1 (0.6)
Rheumatoid arthritis	1 (0.6)
Sarcoidosis	1 (0.6)
Scleroderma/morphea	1 (0.6)
Sjogren's syndrome	1 (0.6)
Type 1 diabetes mellitus	1 (0.6)
Undifferentiated connective tissue disease	1 (0.6)

3.3 | Autoimmune Serology

Serological testing was rarely conducted in paediatric patients with VLS. Therefore, analysis was confined to the adult patient group. Autoimmune screening was conducted in 38.3% of patients ($n = 798$), with 42.4% returning an abnormal or positive test result. Antinuclear antibodies (ANA) were found in 31.0% of tested patients (Table 5). Speckled and homogenous were the most frequent ANA patterns (Table 5). Most patients had ANA titres less than or equal to 1:160 (Table 5). Thyroid stimulating hormone level (TSH) was abnormal in 8.2% of patients (Table 5). Thyroid peroxidase antibodies and thyroglobulin antibodies occurred in 16.1% and 18.9% of patients, respectively, and an abnormal thyroxine (T4) level was seen in 5.5% of patients tested (Table 5).

A small subset of patients with VLS underwent further autoimmune investigations. A low vitamin B12 level occurred in 5.9% of patients (Table 5). Intrinsic factor antibodies were observed in one patient, and gastric parietal cell antibodies occurred in 5.3% of cases (Table 5). There was a comparable prevalence of positive autoimmune serology between the total adult population, and those with a positive family or personal history of autoimmunity ($n = 350$), suggesting it is worthwhile to screen all patients with VLS (Table 5). However, in the group with an autoimmune history there was a higher prevalence of gastric parietal cell antibodies (9.5%).

TABLE 4 | The prevalence of autoimmune diseases in relatives of patients diagnosed with vulvar lichen sclerosus as adults, defined as > 12 years of age ($n = 2084$).

Autoimmune disease	Number (%)
Autoimmune thyroid disease (not specified)	50 (2.4)
Psoriasis	50 (2.4)
Rheumatoid arthritis	15 (0.7)
Hashimoto's thyroiditis	11 (0.5)
Vitiligo	10 (0.5)
Lichen planus	8 (0.4)
Graves' disease	7 (0.3)
Coeliac disease	6 (0.3)
Crohn's disease	6 (0.3)
Pernicious anaemia	5 (0.2)
Scleroderma/morphea	5 (0.2)
Systemic lupus erythematosus (SLE)	5 (0.2)
Polymyalgia rheumatica	4 (0.2)
Multiple sclerosus	3 (0.1)
Type 1 diabetes mellitus	3 (0.1)
Addison's disease	2 (0.1)
Sjogren's syndrome	2 (0.1)
Ulcerative colitis	2 (0.1)
Alopecia areata	1 (0.0)
Ankylosing spondylitis	1 (0.0)
Autoimmune iritis	1 (0.0)
Bullous pemphigoid	1 (0.0)
Granulomatous with polyangiitis	1 (0.0)
Sarcoidosis	1 (0.0)

4 | Discussion

In this retrospective cohort study, we have shown that a significant proportion of adult and paediatric patients with VLS have an associated autoimmune condition. The most prevalent autoimmune diseases associated with VLS were psoriasis, Hashimoto's thyroiditis, lichen planus, vitiligo, and Graves' disease. A total of 8% of VLS patients tested had abnormal thyroid function, and 20% had thyroid antibodies.

A similar prevalence of autoimmune disease has been observed in children diagnosed with VLS [2, 26]. In our study, the most prevalent autoimmune diseases in patients diagnosed as children were psoriasis, vitiligo and Hashimoto's thyroiditis. Similar frequencies of vitiligo [2, 26] and thyroid disease [2] have also been reported in small studies. No previous paediatric studies have noted psoriasis as a prevalent autoimmune disease [2, 23, 26]. Clinicians in our study specifically enquired about psoriasis and examined for psoriatic plaques. In the other studies, a standardised patient questionnaire was used to determine coexisting autoimmune disease, and it is likely patients did not consider psoriasis [2, 26]. Additionally, it is unclear whether dermatological examinations in these studies were restricted to the vulvar region and therefore not likely to visualise signs of psoriasis elsewhere [2, 23].

In patients diagnosed as children, a family history of autoimmune disease was more common than in adults. Similarly, a greater percentage of children had a family history of lichen sclerosus compared to patients diagnosed as adults. To our knowledge, no studies have compared family history between paediatric and adult patients with VLS. The rates of familial lichen sclerosus in our adult population are consistent with other studies [7, 8]. A large retrospective study that analysed adults and children together reported that 12% of patients had a family history of lichen sclerosus [10]. They also described an increased prevalence of autoimmune disease in patients with familial lichen sclerosus compared to those with sporadic disease, although this trend was not significant [10]. This might suggest that there is a stronger genetic influence in children leading to earlier onset of VLS.

The high prevalence of autoimmune disease in adults in this study is generally consistent with previous reported rates [13, 27]. However, some studies have described lower rates [5, 14, 19]. We reported that the most common autoimmune diseases were psoriasis, Hashimoto's thyroiditis and lichen planus. The frequency of psoriasis was similar to that reported by another dermatological study which involved comprehensive history-taking and skin examination [8]. Some retrospective or patient self-reported questionnaire studies have reported a lower prevalence of psoriasis [12, 28, 29].

The prevalence of Hashimoto's disease and Graves' disease in our cohort were very similar to those described in a recent, large study and higher than seen in their control group [12], and the proportion of positive thyroid antibodies in patients with VLS in this study was consistent with previous investigations [8, 20, 21]. Older and smaller studies have reported higher rates of these antibodies, and this may reflect changes that have occurred in laboratory testing [13, 18, 19]. Abnormal thyroid function was observed in 8.2% of our cohort, as assessed by levels of thyroid stimulating hormone. Most female studies have reported thyroid autoantibody levels, and to our knowledge none have reported thyroid function. One study reported that 5.0% of males with lichen sclerosus had abnormal thyroid function [30]. In our study, the relatively high rate of positive anti-nuclear antibody serology was consistent with one lichen sclerosus study [13], and similar to the rates reported in the general population [31]. These antibodies have a high false positive rate and can be positive in a variety of clinical scenarios [31]. Therefore, testing for anti-nuclear antibodies is of limited benefit.

There were limitations to this retrospective study. Retrospective designs are limited by the information contained within prior clinical records. In our study, many patients had hypothyroidism or hyperthyroidism recorded without a statement on the underlying mechanism. This likely resulted in autoimmune thyroid disease being underreported. In the adult cohort with an autoimmune history, only 38.3% of patients received autoimmune

TABLE 5 | The prevalence of positive autoimmune serology and blood tests in adult patients with vulvar lichen sclerosus. Prevalence was determined across all patients ($n = 798$), and for a subset of patients with a personal or familial history of autoimmunity ($n = 350$). Adults were defined as > 12 years of age.

	All patients		Patients with an autoimmune history	
Test	**Number tested**	**Number of positive tests (%)**	**Number tested**	**Number of positive tests (%)**
Abnormal thyroid stimulating hormone (TSH) level	644	53 (8.2)	297	38 (12.8)
Abnormal thyroxine (T4) level	109	6 (5.5)	65	4 (6.2)
Abnormal triiodothyronine (T3) level	62	0	43	0
Thyroid peroxidase antibody	679	109 (16.1)	272	59 (21.7)
Thyroglobulin antibody	682	129 (18.9)	274	59 (21.5)
Low vitamin B12	186	11 (5.9)	87	6 (6.9)
Low active B12	54	4 (7.4)	21	1 (4.8)
Intrinsic factor antibody	100	1 (1.0)	40	1 (2.5)
Gastric parietal cell antibody	94	5 (5.3)	42	4 (9.5)
Antinuclear antibodies (ANA)	568	176 (31.0)	256	82 (32.0)
ANA Pattern	173		80	
Speckled		75 (43.4)		32 (40.0)
Homogenous		57 (32.9)		26 (32.5)
Nucleolar		16 (9.2)		8 (10.0)
Centromere		2 (1.2)		2 (2.5)
Spindle		1 (0.6)		1 (1.3)
Mixed pattern		22 (12.7)		11 (13.8)
ANA Titre	173		82	
1:40		50 (28.4)		19 (23.2)
1:80		34 (19.3)		13 (15.9)
1:160		55 (31.3)		30 (36.6)
1:320		10 (5.7)		7 (8.5)
1:640		14 (8.0)		5 (6.1)
1:1280		5 (2.8)		5 (6.1)
1:2560		5 (2.8)		3 (3.7)
Extractable nuclear antigen (ENA)	134	3 (2.2)	73	3 (4.1)
ENA Type	3		3	
SSA-Ab		2		2
SSB-Ab		1		1
Double-stranded DNA antibody	94	3 (3.2)	43	1 (2.3)
Smooth muscle antibody	87	6 (6.9)	36	3 (8.3)
Anti-cyclic citrullinated peptide (anti-CCP) antibody	96	0	44	0
Rheumatoid factor	24	4 (16.7)	21	3 (14.3)

(Continues)

TABLE 5 | (Continued)

Test	All patients		Patients with an autoimmune history	
	Number tested	Number of positive tests (%)	Number tested	Number of positive tests (%)
Deaminated gliadin peptide antibodies and/or tissue transglutaminase antibodies	71	4 (5.6)	40	4 (10.0)
Coeliac human leukocyte antigens HLA-DQ2 or -DQ8	10	7	10	7
HLA-B27	5	4	4	3

serology testing, limiting the scope of this study. An additional limitation was that only anti-nuclear and thyroid antibody testing were conducted routinely in this cohort. We found that 5.3% of patients had gastric parietal cell antibodies and 5.9% had a low vitamin B12 level. The prevalence of pernicious anaemia in the general population is 0.1% [16]. Pernicious anaemia is a risk factor for iron deficiency and gastric adenocarcinoma, and gastroscopy is recommended by international guidelines to assess and stage gastric atrophy, possibly followed by endoscopic surveillance [32]. Thus, a diagnosis of pernicious anaemia would change patient management and justifies out suggestion of screening for pernicious anaemia based on the results of our study.

Future work should investigate whether there is a common aetiology between lichen sclerosus and other autoimmune skin disorders like lichen planus and psoriasis. As there is compelling evidence of an increased prevalence of thyroid disease in VLS, it may be worthwhile to determine the incidence of VLS in autoimmune thyroid disease. This research would inform holistic clinical care and determine whether patients with autoimmune thyroid disease should be asked about vulvar symptoms or examined for signs of VLS.

5 | Conclusions

This work provides further evidence of an association between VLS and thyroid disease, psoriasis, lichen planus, vitiligo and pernicious anaemia. This study suggests that it is worthwhile screening for thyroid disease in this population due to the relatively high prevalence of thyroid disease within this group. Given 5.3% of patients had positive gastric parietal cell antibodies and 5.9% had a low vitamin B12, testing for pernicious anaemia is recommended. Antinuclear antibody screening in asymptomatic patients with VLS is uninformative, with many patients returning a non-specific, low antibody titre. Initial autoimmune screening in VLS can be rationalised to TSH, vitamin B12 levels, intrinsic factor and parietal cell antibodies. Thyroid antibody testing should be performed in hypothyroid patients.

Author Contributions

Conceptualization: Rebecca Bronwyn Saunderson and Gayle O Fischer. Methodology: Rebecca Bronwyn Saunderson, Marlene Wijaya, Annabel Guttentag. Formal analysis and investigation: Annabel Guttentag. Writing – original draft preparation: Annabel Guttentag. Writing – review and editing: Rebecca Bronwyn Saunderson, Annabel Guttentag, Gayle O Fischer, Angela Lee, Ken Liu and Marlene Wijaya. Resources: Rebecca Bronwyn Saunderson and Gayle O Fischer.

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Ethics Statement

This study received ethics approval from the Human Research and Ethics Committee of the Northern Sydney Local Health District (2023/ETH00719).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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