Case report

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Lichen sclerosis and data science: using an age, site and gender specific disease to define correlation and causality

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Abstract

Introduction: Lichen sclerosis (LS) is a site, gender and age specific disease that affects the vulvar region of menopausal women. The menopausal transition is characterized by physiologic changes that impact basic processes, such as weight, sleep and drug clearance. Our current pharmacopeia includes drugs that target basic metabolic processes such as cholesterol, sex steroidogenesis and the gut microbiome. Introduction of drugs engages complex pathways that govern bile salt metabolism and the provision of sex steroid substrate. We hypothesized that lichen sclerosis in the vulva may represent an off target effect of pharmaceutical alteration of sex steroid substrate in some women. We compared biometric and drug data in women with lichen sclerosis with an age matched control group without disease.

Methods: 43 women with lichen sclerosis underwent chart review to determine BMI, Fitzpatrick level, and pharmaceutical burden. This data was compared to 106 randomly selected age matched controls. Logistic regression was adjusted for age, BMI and Fitzpatrick photo typing. The statistical software was R version 3.0.1. Cases were defined as those with diagnosis claims for lichen sclerosis and were obtained from electronic records in a single private practice.

Results: Proton pump inhibitors were noted in 12/43 women (28%) cases and 15/106 (14%) controls: $p=0.048$, (confidence interval $CI=-0.01$ to 0.287), adjusted p value 0.33 ; Hormone therapy 5/43 cases (12%), 26/106 (25%) controls: p value 0.078 , ($CI=-0.25$ to 0.002), adjusted p value 0.02 . Antihypertensive medications 17/43 (40%) cases, 29/106 (27%) controls, p value 0.14 , ($CI=-0.047$ to 0.29), adjusted p value 0.8 . Statins 16/43 cases (37%), 28/106 controls (26%); $p=0.19$, ($CI=-0.05$ to 0.27), adjusted p value 0.89 . Average age among cases was 63, average age in the control group was 61. Average BMI was 27.5 in the case group, 23.6 in the control group. Logistic regression analysis was adjusted for age, BMI and Fitzpatrick phototyping.

Conclusions: Borderline statistical significance was seen with proton pump inhibitors and hormone replacement therapy (HRT). The significance seen with proton pump inhibitors went away with adjustment for Fitzpatrick, age and BMI. The significance seen with HRT withstood adjustment, with the control group featuring more women on hormone replacement therapy than the case group.

Keywords: Fitzpatrick phototyping, lichen sclerosis, polypharmacy, drug metabolism

Case presentation

Menopause is characterized by physiologic changes that alter sleep, salt and water metabolism, insulin resistance and drug metabolism [1,2]. Drug metabolism is a complex, overlapping and competitive process that utilizes key components of cholesterol and bile metabolism [3-7]. The transport mechanisms for endogenous steroids also function in the delivery and elimination

of HMG-CoA reductase inhibitors (statins), angiotensin receptor II antagonists and cardiac glycosides [8,9]. We hypothesized that lichen sclerosis may relate to competition in steroid and drug transport mechanisms at a time of physiologic change.

7 of the 43 women in this case series suspected that a recent drug change caused the problem; 3 with change in hormones, 3 with introduction of a beta blocker and 1 with introduction of

thyroid replacement. This number is probably low, as approximately half of these patients were seen years after their initial diagnosis and could not remember the sequence of events. Many underwent months and years of treatment for other vulvar conditions, such as chronic yeast infections, before the characteristic features of lichen sclerosus emerged (**Figures 1-4**).

86% of the patients were on at least one drug, with 58% on more than one drug. Hypertension was the most treated comorbid state with over half of this group on a beta blocker. 37% were on HMGCoA reductase inhibitors and 33% were on a drug (s) that targets the gut. Three women were extreme athletes with chronic amenorrhea. 79% were very fair, Fitzpatrick phototyping classification 1 or 2. 60% had a BMI>25.

All patients were counseled about the effect of diet and exercise on the need for prescription drugs. Patients with

Figure 1. Drug eruption: 89 year old with polypharmacy and two year history of painful dermatitis superimposed on lichen sclerosus.

Figure 2. Drug eruption: 89 year old 4 weeks after cardiologist guided cessation of amiodarone, amlodipine and omeprazole.

Figure 3. Lichen Sclerosus: 70 year old obese female presenting with lichen sclerosus after weaning Premarin.

Figure 4. Lichen Sclerosus: 70 year old after applying pioglitazone in ointment.

high BMI and those with a history of large for gestational age babies (LGA) were offered low dose metformin. Patients with severe disease resistant to clobetasol were given topical pioglitazone 30mg/loz of petrolatum [10] (**Tables 1 and 2**).

Table 1. Lichen Sclerosus: drug and biometric data in 43 women.

Lichen sclerosis	No=43	%
Age over 50	41/43	95%
Fitzpatrick phototyping 1-2*	34/43	79%
BMI>25	26/43	60%
Beta blockers	10/43	23%
All antihypertensives	23/43	53%
statins	17/43	14%
SSRI's	2/43	5%
PPI	14/43	33%
SERM	2/43	5%
More than one drug	25/43	58%
No drug at onset	6/43	14%
Onset at time of drug change**	7/43	16%

SSRI: Serotonin reuptake inhibitor; PPI: Proton pump inhibitors; SERM: Selective estrogen receptor modulator
*included as a potential biomarker of genetic variation in aromatase; **These women were seen early in the course of their disease and felt the lichen sclerosis was related to introduction or withdrawal of a drug.

Table 2. Lichen Sclerosus: suggested treatment algorithm for women presenting at midlife.

Drug → → drug reduction → → topical pioglitazone
LSA →
No drug → → BMI>25, LGA, GDM → → metformin → → topical pioglitazone

BMI: Body mass index; LGA: Large gestational age;
GDM: Gestational diabetes

Discussion

The nuclear receptors that control cholesterol and bile metabolism have important functions in sex steroid substrate provision and drug clearance [11]. Older views of drug metabolism focused on the p450 system and fall short in predicting the variability in drug response seen in patients on multiple medications [12]. New information on transporter mechanisms, which have substrate and end organ specificity, has improved our understanding of inter-organ variability in drug response. Menopause changes cholesterol and bile metabolism and drugs impact key regulators of cholesterol and bile metabolism [13,14]. Bile salts and the gut microbiome provide the steroid substrate precursors essential for steroidogenesis. It may be that specific drugs in combination, such as Hmg-CoA inhibitors (statins) and proton pump inhibitors, may be problematic if introduced at times of physiologic change [15]. Dual drug combinations that require functional cytochrome 3A4 and p-glycoprotein may have difficulty to measure impact at menopause, because women lose a portion of intestinal 3A4 [16].

While antihypertensives, statins and proton pump inhibitors

were all found more frequently in the case group, they did not meet statistical significance. After logistic regression analysis for age, BMI and Fitzpatrick phototyping, only hormone replacement therapy, seen more frequently in the control group, maintained statistical significance.

We were limited by the inability to accurately note the onset of the disease in some women. The difficulties noting onset complicate the definition of a temporal relationship between drug introduction and onset of disease. It may be that multiple requests for treatment for yeast infections may be a curatable measurement for the onset of lichen sclerosis. In some women, lichen sclerosis is asymptomatic and only recognized on physical exam.

Concurrent changes in medical care could impact the frequency of this disease. Polypharmacy accelerates around the menopausal transition. The utilization of hormone replacement therapy is more controversial. Older, sicker and heavier women often bypass well woman exams and forego discussions on hormone replacement therapy. Off target effects of statins and proton pump inhibitors, introduced in 1987 and 1990, respectively, on diabetes risk and the gut microbiome, are more recent findings.

The work-up of patients presenting with lichen sclerosis should include a complete drug history. Advances in pharmacokinetics pertaining to gender may improve prescribing habits at menopause. Treatments offered to women with lichen sclerosis may include reduction of comorbid states through non pharmaceutical methods, reduction of specific drugs and identification of harmful drug/drug combinations at menopause.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	CMR	RC
Research concept and design	✓	--
Collection and/or assembly of data	✓	✓
Data analysis and interpretation	✓	✓
Writing the article	✓	✓
Critical revision of the article	✓	--
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Statistical analysis	✓	--

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