

Report

Understanding the role of cutaneous allergy testing in anogenital dermatoses: a retrospective evaluation of contact sensitization in anogenital dermatoses

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Abstract

Background Patients with anogenital symptoms may delay before seeking medical attention. Attempted self-treatment with multiple topical preparations and excessive hygiene measures offer ideal conditions for sensitization. The aim of this study was to identify the common allergens detected on cutaneous allergy testing in patients presenting with anogenital symptoms.

Methods A retrospective chart review of patients who underwent cutaneous allergy testing for perianal and/or genital symptoms over a 3-year period, January 2013 to December 2015, $n = 99$. Information was gathered from medical records, pretesting questionnaires, and cutaneous allergy testing records.

Results At least one relevant allergen(s) was identified in 44/99 (45%) in our cohort, with allergic reactions to fragrances, *Myroxylon pereirae*, caine mix, sodium metabisulfite, and methylisothiazolinone most frequently observed.

Conclusions Cutaneous allergy testing is a useful investigation in patients presenting with anogenital symptoms, but advice regarding general skin care measures should not be omitted. The most commonly identified relevant allergens in our study were those present in over-the-counter cleansing and hemorrhoid preparations.

Introduction

Anogenital cutaneous symptoms may cause significant distress and can be challenging to diagnose and treat. Patients with anogenital itch and/or rash present to many specialties including primary care, gastroenterology, colorectal surgery, gynecology, and dermatology. Typically, patients have been symptomatic for many years and have used a variety of over-the-counter preparations, prior to seeking an expert opinion.^{1,2}

The differential diagnosis of anogenital itch includes lichen sclerosis, psoriasis, atopic eczema, seborrheic dermatitis, lichen simplex chronicus, and contact dermatitis, both of irritant and allergic etiology. Anogenital skin is susceptible to irritant dermatitis because of persistent occlusion, friction, sweating, and local secretions. This provides an ideal environment for the development of allergic contact dermatitis (ACD). Previous studies have reported rates of ACD of 29–54% in patients investigated with cutaneous allergy testing for vulval symptoms and in up to 63% in patients with anogenital symptoms.^{1–9}

Allergic contact dermatitis may occur as a primary disorder or may coexist with an underlying dermatosis because of impaired integrity of the skin barrier and the application of topical treatments. Cutaneous allergy testing should be considered early in the assessment of patients with chronic anogenital symptoms of itch and irritation. In patients with persistent symptoms, despite optimization of anogenital skin care and avoidance of irritants and allergens, referral to gastroenterology or colorectal surgery should be arranged for assessment and possible lower gastrointestinal endoscopy to investigate for malignancy.

While it has long been recognized that hemorrhoid creams contain contact allergens, there are many products specifically marketed for cleansing anogenital skin available over the counter including cleansing wipes, washes, and freshening sprays, which may contain active ingredients and excipients that are potential contact allergens. Topical treatments, prescribed or over-the-counter, are used in over half of patients with anogenital complaints prior to attending dermatology.¹⁰

The aim of this retrospective cohort study was to identify the common allergens detected on cutaneous allergy testing in patients presenting with anogenital symptoms.

Materials and Methods

Data for all ($n = 753$) patients who attended for cutaneous allergy testing in the dermatology department between January 2013 and December 2015 were analyzed. Of these 753 patients, 99 (13%) presented with anogenital symptoms.

IQ Ultra chambers were used, and if not tolerated, Finn chambers with Scanpore tape were substituted, and results were read on day 2 (after 48 hours) and day 4 (after 96 hours) according to the International Contact Dermatitis Research Group criteria. All patients were tested to the British Society for Cutaneous Allergy standard series with the addition of Limonene oxidized 0.3% and Linalool oxidized 1%. Other series are added based on the clinical history. Additional series tested included the following: medicaments series in 69, fragrances in 64, textiles in 36, cosmetics series in 31, caine mix in 10, own products in nine, corticosteroids in six, acrylates in four, and carba mix in four patients. Full details of the allergens in the series used are provided in Appendix 1. Allergic reactions are graded from + (erythema) to +++ (bullous) and are considered to be of current relevance if there is a clear relationship between the presenting complaint and exposure to the suspected allergen.

Results

Cutaneous allergy testing was performed in 99 patients, 59 female and 40 male, presenting with anogenital symptoms, with an average age of 47.6 years (range 17.3–81.8 years) over a 3-year period from January 2013 to December 2015 inclusive. The average duration of symptoms in our cohort was 5.5 years (range 0.5–30 years). All patients were tested to the standard series, 93/99 patients were tested to additional series.

Allergic reactions were observed in 67/99 patients (Table 1). The range of positive allergens was 1–15 (mean 1.8). Cutaneous allergy testing identified ≥ 1 allergen in 42/67 (63%) patients.

Contact allergens considered of current clinical relevance for anogenital symptoms were identified in 45/67 (67%) patients with a positive reaction, 45% of the total cohort. Other allergens identified were considered of past relevance, uncertain relevance or not relevant, e.g. nickel, cobalt, potassium dichromate, disperse orange, and paraphenylenediamine (PPD). Nickel was the most frequent allergen identified, 32/67 patients, although it was deemed not of current relevance in all cases.

In patients with relevant allergens ($n = 45$), the most frequent allergens identified were medicaments in 22 (49%) and fragrances in 19 patients (42%). Reactions to ≥ 5 allergens were seen in 8/67 (12%) patients with an average duration of

symptoms of 7.5 years. The allergens observed most frequently in this subgroup were fragrances (4), local anesthetics (4), *Myroxylon pereirae* (4), antibiotics (4), and methylisothiazolinone (MI) (3). One patient had reactions to five antimicrobial agents (neomycin, bacitracin, gentamicin, framycetin, polymyxin).

One of the authors (CF) collected data looking at ingredients in cleansing and freshening products marketed for anogenital skin and available over the counter in community pharmacies. Many of these widely available products (Table 2), in addition to hemorrhoid creams, contain recognized contact allergens including preservatives (parabens, benzoic acid, sodium

Table 1 Allergens identified in our patients with anogenital symptoms

Allergen	<i>n</i>
Nickel sulphate hexahydrate 5%	32
Medicaments ^a	22
Multiple	10
<i>Myroxylon pereirae</i> 25% ^a	13
Caine mix 10% ^a	10
Neomycin sulphate 20% ^a	4
Framycetin sulphate 10% ^a	3
Colophony 20%	2
Quinoline mix 6%	1
Fragrances ^a	19
Multiple	7
Limonene oxidized 0.3% ^a	9
Linalool oxidized 1% ^a	6
Isoeugenol 2% ^a	2
Sodium metabisulfite 1% ^a	8
Cobalt (II) chloride hexahydrate 1%	8
Methylisothiazolinone 0.2% ^a	5
Methylisothiazolinone & Methylchlorisothiazolinone 0.02% ^a	3
Formaldehyde 2% ^a	2
Glyceryl monoethioglycolate 1%	1
t-Butyl hydroquinone 1%	1

^aRelevant allergens in some patients with anogenital symptoms based on clinical correlation.

Table 2 Allergens present in commonly used anogenital topical preparations

Allergen	Products
Balsam of Peru	Anusol
EDTA	Preparation H, Vagisil
Lidocaine	Boots Haemorrhoid Relief, Germoloids
Benzocaine/Cinchocaine	Proctosedyl, Vagisil
Diazolidynl urea	Preparation H Wipes
Wool fats	Anusol, Proctosedyl
Framycetin sulphate	Proctosedyl
Hydrocortisone	Proctosedyl
Parabens	Anusol, Preparation H (cream/wipes), Vagisil

benzoate, di-/tetrasodium EDTA), fragrances (*Calendula officinalis* Extract), and formaldehyde releasers (imidazolidinyl urea), which may be identified on standard and/or extended series.

Fragrances

In the standard series, 10/99 patients had a positive reaction to fragrance mix I, 8/99 to limonene oxidized, and six to linalool oxidized. There were no positive reactions to fragrance mix II. A further 13/99 patients reacted to *Myroxylon pereirae*, which may be a marker of fragrance allergy and is also present in a number of hemorrhoid preparations. Of 64/99 patients tested to an extended fragrance series (Appendix 1), 11/64 (17%) had positive reactions (four to multiple), of which 10/11 (91%) tested positive to Fragrance mix I or limonene/linalool oxidized in the standard series used. The remaining patient tested positive to isoeugenol (1). Of 19 patients with a relevant fragrance allergen identified, eight (42%) were identified on the standard series only (of which six had an extended fragrance series applied), 10 (53%) were identified on both standard and extended fragrance series, and one (5%) on extended fragrance series alone.

Medicaments

Allergens present in medicaments were identified as relevant in 22/99 patients and included *Myroxylon pereirae* (13), caine mix III/IV (10), neomycin (4), framycetin (3), colophony (2), gentamicin (2), tixocortol pivalate, bacitracin, and polymixin (1 each). The medicament series was applied in 69 patients, of which four (6%) had a clinically relevant allergen identified, all of whom had been identified in the standard series and had multiple clinically relevant allergens, including neomycin, framycetin, gentamicin, caine mix/dibucaine, and proctosedyl®.

Comment

Anogenital skin, in particular vulval skin, has been shown to react more intensely to irritants than other skin areas.^{11–14} Skin in this area is vulnerable to sensitization because of occlusion, friction, and exposure to irritants such as sweat, urine, vaginal/urethral secretions, and fecal matter. The addition of a chronic inflammatory dermatosis enhances susceptibility to the development of allergic contact dermatitis.

The majority of previously published studies report on either vulval or perianal dermatitis. Warshaw *et al.* reported on 573 patients from the North American Contact Dermatitis Group database with anogenital symptoms and noted that allergens that were significantly more common in patients with anogenital involvement were more likely to be found in products in use in the anogenital area.⁶ There is a myriad of cleansing agents, freshening sprays, and fragranced wipes available commercially marketed for anogenital skin and a perception that 'natural' products are safer than synthetic alternatives. A recent study reported that 42/66 (63.6%) patients with chronic vulval itch had applied natural topical products to the vulva.¹⁵ These "natural" products often contain fragrances and

preservatives, such as MI and sodium metabisulfite, which we found to be clinically relevant allergens in our patients.

The delay to presentation of 5.5 years from onset of symptoms in our cohort is similar to previous reports.^{3,8} This delay provides ample time for exposure to contact allergens in over-the-counter products. Previous studies have demonstrated higher rates of relevant contact allergens with >24 months of symptoms, which would support this.¹⁵ In our cohort, the average duration of symptoms was 2 years longer in patients with reactions to ≥ 5 allergens, 7.5 vs. 5.5 years. Al-Niami *et al.* reported that allergic contact dermatitis is more likely to be diagnosed in patients with symptoms >5 years and those using multiple products.³ Commonly encountered medicated products containing allergens responsible for anogenital allergic contact dermatitis are provided in Table 2. These products are licensed to be used for up to 1 week, but in many cases patients use them intermittently over prolonged periods.

Sulfites are used as preservatives in medicaments, cosmetics, and food. Sodium metabisulfite (SMB) can be found as a stabilizer in anesthetics, topical antifungal, and hemorrhoid creams, and rectal suspensions. Whilst the relevance of SMB reactions was previously controversial, it appears to be relevant in most cases, where there is a positive reaction.^{3,16,17} In a previously published study from our center, sodium metabisulfite (tested at 1% in petrolatum) has been shown to be a relevant contact allergen in vulval and perianal dermatitis.¹⁷

Similar to previous retrospective series, nickel was the commonest allergen identified in our cohort, although it is not felt to be a relevant allergen in patients with anogenital symptoms.³ There has been discussion in the literature regarding perianal exposure to nickel from dietary sources and vulval/perianal exposure from sanitary towels, although this has not been confirmed.¹⁸

Cutaneous allergy testing is the gold standard for the diagnosis of ACD in patients presenting with anogenital symptoms. In addition to patch testing, it is essential that optimization of skin care and careful evaluation of topical preparations in use takes place. In this study, over 50% of patients reported an improvement in symptoms following initial consultation, regardless of the outcome of cutaneous allergy testing.

By its retrospective nature, this study has some limitations. It would be useful to identify the specific over-the-counter and/or cleansing/freshening products used on anogenital skin by patients presenting for patch testing. Patients often use a multitude of products, and careful scrutiny of the ingredient listings is important to assist interpretation of the relevance of allergens detected.

It is essential to correlate results of cutaneous allergy testing with information obtained from thorough history and examination to determine relevance of identified allergens. The most common relevant allergens we identified were fragrances, balsam of peru, topical anesthetics, and antibiotics (neomycin and framycetin) in line with previously published series.^{2,3,19–21} The use of extended series may identify allergens not highlighted with

testing to the standard series only.^{2,11,22} It can be difficult to define the relevance of fragrance allergy in these patients. With the large range of personal hygiene products available, it may be that fragrances are more relevant than previously thought in anogenital ACD.

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Appendix 1: Series tested.

Table A1. Standard series

Potassium dichromate 0.5%
Neomycin sulphate 20%
Thiuram mix 1%
4-Phenylenediamine (PPD) 1%
Cobalt (II) chloride hexahydrate 1%
Caine mix III 10%
Formaldehyde 2%
Colophony 20%
Quinoline mix 6%
<i>Myroxylon pereirae</i> (Balsam of Peru) 25%
N-isopropyl-N-phenylenediamine 0.1%
Lanolin alcohol 30%
Mercapto mix 2%
Epoxy resin 1%
Paraben mix 16%
4-tert-butylphenol formaldehyde resin (PTBP) 1%
Fragrance mix I 8%
Quaternium 15 1%
Nickel sulphate hexahydrate 5%
Budesonide 0.1%
Methylisothiazolinone + Methylchlorisothiazolinone 0.02%
Mercaptobenzothiazole 2%
Amerchol L 101 50%
Sesquiterpene lactone mix 0.1%
4-Chloro-3-cresol 1%
2-Bromo-2-nitropane-1,3-diol (bronopol) 0.5%
Cetearyl alcohol 20%
Fusidic acid sodium salt 2%
Tixocortol-21-pivalate 1%
Imidazolidinyl urea 2%
Diazolidinyl urea 2%
Methyldibromo glutaronitrile 0.3%
Ethylenediamine dihydrochloride 1%
Chloroxylenol (PCMX) 0.5%
Carba mix 3%
Fragrance mix II 14%
Disperse blue mix 106/124 1%
Lylal 5%
Caine mix IV 10%
Sodium metabisulfite 1%
Compositae mix 2.5%
Methylisothiazolinone 0.2%
Limonene oxidized 0.3%
Linalool oxidized 1%

Table A2. Fragrances and essential oils series

Cinnamic aldehyde 1%
Cinnamic alcohol 2%
Amylcinnamaldehyde 2%
Isoeugenol 2%
Eugenol 2%
Geraniol 2%
Oakmoss absolute 2%
Hydroxycitronellal 2%
Narcissus absolute 2%
Musk xylene 1%
Methyl anthranilate 5%
Musk moskene 1%
Mush ketone 1%
Jasmine synthetic 2%
Benzyl salicylate 10%
Benzyl alcohol 10%
Vanillin 10%
Lavender absolute 2%
Cananga oil 2%
Rose oil, Bulgarian 2%
Ylang-ylang oil 2%
Geranium oil Bourbon 2%
Jasmine absolute, Egyptian 2%
Sandalwood oil 2%
Citral 2%
Farnesol 5%
Citronellol 1%
Hexyl cinnamic aldehyde 10%
Coumarine 5%
Linalool 10%
Dipentene (di-Limonene) 2%
Majantole 5%
Taraxacum officinale (Dandelion) 2.5%
Evernia furfuracea 1%

Table A3. Medicaments series

Miconazole 1%
Bacitracin 5%
Chloramphenicol 5%
Clotrimazole 5%
Gentamicin sulphate 20%
Benzalkonium chloride 0.1%
Econazole nitrate 1%
Chlorhexidine digluconate 0.5%
Sorbic acid 2%
Coal tar 5%
Nystatin 2%
Propylene glycol 5%
Sorbitan sesquileate 20%
Triclosan (Irgasan DP 300) 2%
2,6-Di-tert-butyl-4-cresol (BHT) 2%
2-Tert-butyl-4-methoxyphenol (BHA) 2%
Framycetin sulphate 10%
Polymixin B sulphate 3%
Granuflex dressing (as is)

Table A4. Cosmetic and facial series

2-Di-tert-butyl-4-cresol (BHT) 2%
2-Tert-butyl-4-methoxyphenol (BHA) 2%
Toluenesulfonamide-formaldehyde resin 10%
Cocamidopropyl betaine 1%
Sorbic acid 2%
t-Butyl hydroquinone 1%
Triclosan (Irgasan DP 300) 2%
Propyl gallate 1%
Abitol 10%
Benzyl alcohol 10%
Benzophenone-3 10%
Triethanolamine 2%
DMDM hydantoin 2%
Tea tree oil 5%
Chloroacetamide 0.2%
Iodopropynyl butylcarbamate 0.2%
Oleamidopropyl dimethylamine
Sorbitan sesquileate 20%
Cocamide Dea 0.5%
Glyceryl monothioglycolate 1%
Butyl-methoxy-dibenzoylmethane (Parsol 1789) 10%
Aluminium chloride hexahydrate 2%
Propolis 10%
Dexpanthenol 5%

Table A5. Textiles and dyes series

Disperse yellow 3 1%
Disperse orange 3 1%
Disperse red 1 1%
Disperse red 17 1%
Disperse blue 153 1%
Disperse blue 3 1%
Disperse blue 35 1%
Dimethylol dihydroxyethyleneurea 4.5%
Dimethyl dihydroxyethyleneurea 4.5%
Dimethyl dihydroxyethyleneurea modified (fixECO) 5%
Disperse blue 106 1%
Ethylene urea melanineformaldehyde (Fix AC) 5%
Urea formaldehyde (Kaurit S) 10%
Melamine formaldehyde (Kaurit M70) 7%
Disperse blue 85 1%
Disperse orange 1 1%
Acid yellow 61 5%
Disperse brown 1 1%
Disperse yellow 9 1%
Disperse blue 124 1%
Basic red 46 1%
Reactive black 5 1%
Reactive blue 21 1%
Reactive blue 238 1%
Reactive orange 107 1%
Reactive red 123 1%
Reactive red 238 1%
Reactive red 228 1%
Reactive violet 5 1%
Acid red 118 5%
Direct orange 34 5%
Acid red 359 5%
Dimethyl fumarate 0.1%
Dimethyl fumarate 0.01%
